UNIT TWO LESSON: ADULT STEM CELLS, HOMEOSTASIS and REGENERATIVE MEDICINE

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California State Standards

Biology/Life Science

1.a. Students know cells are enclosed within semi-permeable membranes that regulate their interaction with their surroundings.

4.d. Students know specialization of cells in multi-cellular organisms is usually due to different patterns of gene expression rather than to differences of the genes themselves.

9. As a result of the coordinated structures and functions of organ systems, the internal environment of the human body remains relatively stable (homeostatic) despite changes in the outside environment.

Investigation and Experimentation

1.k. Recognize the cumulative nature of scientific evidence.

1.m. Investigate a science-based societal issue by researching the literature, analyzing data, and communicating the findings.

Goals

- Understand the difference between adult and embryonic stem cells.
- Understand the diversity of adult stem cells and their functions in the body.
- Understand how adult stem cells assist in homeostatic regulation in the body.
- Understand how current research of adult stem cells translates to drug development and cell-based therapies.

Objectives

1. The student will be able to demonstrate adult stem cells' role in regeneration in other animal species.
2. The student will be able to demonstrate where adult stem cells are located in the body and realize that we may discover more types of stem cells in the future.

3. The student will be able to describe homeostasis.

4. The student will be able to explain the role of adult stem cells in homeostatic maintenance of the body.

5. The student will be able to differentiate between embryonic stem cells, adult stem cells, and progenitor cells.

6. The student will be able to research how adult stem cells are currently being used to treat disease and which are in clinical trials.

7. The student will be able to identify the steps of a clinical trial and why this process is relevant to regenerative medicine.

8. The student will be able to distinguish between clinical-trial proven therapies and those offered without scientific evidence.

Outline of Unit 2

I. Invitation

A. What do sea star arms (star fish), lizard tails, and your liver have in common? After reading, discuss myth and questions with students.

1. Prometheus (bird eats liver every day – then liver re-grows every night)
   a. Why would the liver need to regenerate?
   b. Do you think this will ever be possible for humans or other animals?

2. Article with graphics about the myth:
   Prometheus myth

3. Did ancient Greeks know about liver regeneration?
   Free pdf of article (AP extension or teacher background)
   Greek myth and science of regeneration

SYNOPSIS of the Myth of Prometheus: Epimetheus and Prometheus, Titans, aid Zeus in a war against Atlas and the rest of the Titans. Zeus wins and grants the two Titans the ability to create creatures to populate Earth. Epimetheus gives like strength and flight to animals—leaving no good attribute for men. Prometheus gives men the ability to walk upright, and to look towards Olympus. He also gives men fire, but tricks Zeus into accepting the inedible parts of animal sacrifices. Zeus, angered at Prometheus, takes fire away from Man! But Prometheus steals it back. Zeus punishes Prometheus by chaining him onto the Andes Mountains and having an Eagle eat his liver every day. However, Promethius' liver grows back every night. Zeus finally takes pity and allows Chiron (an Immortal Centaur in excruciating pain from Heracles' poison arrow) to sacrifice himself for Prometheus' freedom. Heracles kills the eagle, and everyone is happy.

B. What cells in your body are responsible for regeneration?

1. Where are they? Survey what students think. Use anatomically correct black-line masters of male and female body and record student answers, or do this on board.
   Black LIne Masters

2. Discuss results of this survey as a class
   a. For beginning students, it is safe to say that there are "regenerative" cells EVERYWHERE in the body except the pancreas. Mention the major adult stem cell types: hematopoietic, mesenchymal, and neural.
   b. For more advanced students, you can discuss hematopoietic, mesenchymal, neural, endothelial, and epithelial stem cells and locations from the Teacher Background Information section or the supplementary PowerPoint

3. Discussion following reading of article summaries (below). Any putative stem cell populations? Where haven't we found stem cells? Do all stem cells participate in regeneration?
   a. Horizontal basal cells in the Olfactory bulb: abstract and full text from Abstract and text (advanced)
   Abstract and *summary* of text (easier)
      i. Which type of olfactory bulb cell in the stem cell is controversial?
   b. Kidney stem cells: Abstract and whole text from
      Kidney stem cells article
      i. Presence of stem cells controversial and function unknown.
   c. Retinal SCs: News article
      i. Retinal stem cells article
      Claims retina has stem cells

4. **AP extension:** how do scientists identify stem cells? What are the characteristics of a stem cell? Use above papers and this paragraph from Wikipedia: Stem Cells

Identification
The practical definition of a stem cell is the functional definition - a cell that has the potential to regenerate tissue over a lifetime. For example, the gold standard test for a bone marrow or hematopoietic stem cell (HSC) is the ability to transplant one cell and save an individual without HSCs. In this case, a stem cell must be able to produce new blood cells and immune cells over a long term, demonstrating potency. It should also be possible to isolate stem cells from the transplanted individual, which can themselves be transplanted into another individual without HSCs, demonstrating that the stem cell was able to self-renew. Properties of stem cells can be illustrated *in vitro*, using methods such as *clonogenic assays*, where single cells are characterized by their ability to differentiate and self-renew. As well, stem cells can be isolated based on a distinctive set of cell surface markers. However, *in vitro* culture conditions can alter the behavior of cells, making it unclear whether the cells will behave in a similar manner *in vivo*. Considerable debate exists whether some proposed adult cell populations are truly stem cells.

C. Discuss similarities and differences between wound healing and regeneration.

1. Download HHMI lectures:
HHMI Lectures-Stem cells
View Lecture 2, Adult Stem Cells and Regeneration

2. Use HHMI video adult stem cells handout (student version) for student use as they watch the lecture. See teacher version for answer key.
Download Appendix A student version
Download Appendix A teacher answer sheet

SYNOPSIS: Wound healing uses blood clotting factors (CF's) and hormone/protein signals, like Thrombin, to recruit layers of platelet cell, which clog the wound, allowing the dermis/capillary to re-grow over the wound. This re-growth can use stem cells, but isn't largely due to stem cell division. [Note: adult stem cells support the constant generation of new cells to replace old, damaged, and dying cells. They also participate in injury repair; for example,when muscle is injected with snake venom, muscle satellite cells (stem cells) divide, migrate to the

injury site, differentiate, and fuse together to form new muscle fibers.] Regeneration can occur due to a limb being severed (as with the newt) or from chemical degradation (as in the liver). In limb regeneration, the wound first heals, then a blastema (group of cells) forms, inside which are differentiating stem cells. In this way, stem cells begin to reform the regenerating body part. Thus, regeneration rather than wound healing Relies much more heavily on stem cell division and differentiation, coupled with molecules which signal regeneration to occur.

II. Exploration

A. What are some different types of stem cells? Study adult vs. embryonic stem cells. (EASY) Interactive animation from – Learn Genetics-University of Utah
Animation download

Note: Fetal stem cells are *not* typically considered Pluripotent or equivalent to embryonic stem cells. Please clarify this with your students.

1. While viewing the interactive animation, have students fill out "Stem Cells: What are they? A Great Overview!" handout
Download Stem Cells, What Are They handout by clicking the Download file link under stem_cell_basics_worksheet.doc on the top, right

2. Through this, you will explore:
    a. Plasticity: Totipotent vs. Pluripotent vs. Multipotent
    b. Plasticity's underlying process: Differentiation
        i. What drives differentiation? – gene regulation
            (See microenvironment unit)
        ii. AP extension topics (Google)-Things that regulate differentiation:
            Extracellular signals
            Transcription factors and miRNAs
            (**ADVANCED**)
            Epigenetics

3. As they are, adult stem cells are able to produce one or several types of mature cells rather than many types of cells. Remember, pluripotent embryonic stem cells can produce most types of cells, *except* for extra-embryonic cells and placenta cells, and totipotent embryonic stem cells can produce all types of cells, *including* extra-embryonic cells and placenta cells.
    a. Ex. Muscle stem cells cannot create blood, whereas embryonic stem cells can become anything up to a certain time point in their development
    b. Difference between stem cells and progenitor cells
        i. Think of adult stem and progenitor cells as having different levels of potential, based on how many different types of cells they are able to become.
        ii. In reality there is a continuum of plasticity/potency, and scientists have named and characterized just some of the discrete levels.
        iii. An adult stem cell is generally multipotent, while a progenitor cell is generally unipotent.

B. Homeostasis

1. What is homeostasis?
    a. View video from How Stuff Works
    Homeostasis animation
    b. Discussion question: How are these types of homeostasis (e.g., the body's thermostat, glucose/insulin hormone negative feedback) different from the maintenance of cells in tissue homeostasis?

2. Describe adult stem cells' role in human tissue homeostasis

3. Planaria regeneration lab
    a. Watch video as lead in. "Planarian Regeneration and Stem Cells" from Potent Biology: Stem Cells, Cloning, and Regeneration, HHMI Holiday lectures 2006.
    Download here
        i. *Use student questions* that go with the video – "Planarian Regeneration and Stem Cells Video Handout" with teacher version. Downloadable from
        Download Unit 2 Appendix B student version
        Download Unit 2 Appendix B teacher answer sheet

Unit 2 Appendix B

SYNOPSIS: Describes the basic biology of *Planaria*. It has the ability to regenerate any part of its body, down to when it's cut into 279 fragments. Neoblasts (totipotent stem cells) migrate to areas of damage and create specific differentiated cells in order to regenerate the damaged parts of its body. RNAi experiments portray 240 genes involved in regeneration. One molecule *smedwe* is found in Drosophilia stem cells (involved in gonad cells of female fruit flies). Without this protein the *Planaria* die because the head begins to curl inward. In the future these experiments may allow use of *planaria* to identify gene function in humans and vertebrates.

b. *Discussion questions*: Are human adult stem cells equivalent to planaria neoblasts? Do they have the same potential?
Answer: No, planaria neoblasts can regenerate the entire organism while adult stem cells in humans are restricted to regenerating tissue-specific lineages.

c. Wet lab-use the Northwest Association for Biomedical Research intro PowerPoint, lab protocol, and handouts within the Stem Cell Curriculum available for download
http://www.nwabr.org/education/stemcellforum.htm
→ follow the link titled "Click here to submit your information" and be directed to the Stem Cell Curriculum page, then scroll down to see the Planaria lab

d. Materials for NWABR planaria regeneration protocol
i. The brown planaria, *Dugesia tigrina,* and black planaria, *Dugesia dorotocephala,* can be purchased from commercial supply houses, such as **WARDS** and **Boreal/Science Kits**.
Wards
Boreal

C. Regenerative medicine: what is it?

1. Treatment possibilities using adult and embryonic stem cells
    a. Right now, RM is restricted to adult stem cells and drugs associated with them. (Embryonic stem cells have not gotten to the same point in pre-clinical research and clinical trials as certain adult stem cells. There is a pending clinical trial involving Geron's technology which utilizes differentiated embryonic stem cells to treat spinal cord injuries. More information from The Niche blog:
    Technology to treat spinal cord injury

2. Jigsaw activity: What are examples in the natural world of regeneration? How do humans compare? What cells play a role in lizard tail regeneration? What is the goal of regenerative research and medicine?
    a. Lizard tail and salamander limb regeneration
        i. EASY- about reptiles and tail regeneration
        Limb regeneration
        ii. MID- more about caudal autotomy
        Caudal autotomy-click on small printer icon
        iii. CHALLENGING- research on salamander limb regeneration
        Scientific American-Limb regeneration
    b. CHALLENGING overview
        Discover Magazine-How to grow a new limb
    c. Zebrafish limb regeneration and epigenetic control
        i. CHALLENGING
        Science Daily-Zebrafish limb regeneration
    d. "Mighty mouse" with enhanced regenerative capacity
        i. MID- Mice regrow organs
        Mice that regrow organs
        ii. MID- expansion on above and aging
        Regrowth and Aging
    e. Metazoans
        i. MID- Regeneration research quote
        Regeneration quote
    f. Research on Human regeneration
        i. MID- How animal research leads to knowledge

about human regeneration
Animal research and connection to human regeneration

g. MID-heart regeneration
Heart regeneration-Reuters article

D. What are the potential uses of adult stem cells? Students research the topics and take notes in Double Entry Journal. Instructions for journal Unit Two Appendix C

1. Adult stem cell-based therapies that exist today. The possibility of growing organs in the future.
Adult stem cell therapies-Univ of Utah

2. Drugs that affect or target stem cells (breast cancer drug)
Breast cancer drug

3. Using stem cells to test/screen drugs in vitro
Using stem cells to test drugs-Harvard

4. Diagram of potential uses
Potential uses of stem cells

E. Process and importance of clinical trials

1. Explain steps in clinical trials, preclinical through phase 4. See background information section and associated web readings and resources (listed below).

2. Also use the Student handout: Clinical trials information chart (see teacher version for answers) in Appendix D
Unit Two Appendix D: student handout
Unit Two Appendix D: teacher version

3. Web resources
a. MID- overview of adult stem cell clinical trials and some companies involved
Stem cell drugs/therapies next big market
b. MID- explanation of FDA and clinical trials process
Drugs and clinial trials
OR
MID-CHALLENGING- explanation of clinical trial design

Clinical trial design

c. MID- dose response curve
Mid-dose response curve-Merck

d. MID-CHALLENGING – difficulties in bringing research to therapies
Bringing research to therapies-Newsweek

e. MID – can we use undifferentiated embryonic stem cells for therapies?
Undifferentiated embryonic stem cells for therapies?-CIRM

f. The Drug Pipeline
i. Diagram and explanation of drug pipeline Simple pipeline
ii. More complicated FDA pipeline:
Pipeline-Nature Publishing Group

III. Application

A. Clinical trial exercise

1. Use Regenerative medicine and clinical trials research project handout- Appendix E Unit 2
Appendix E: instructions
Appendix E: grading rubric

2. Students choose diseases from 70+ diseases list- Appendix F Unit 2 Appendix F

3. Students do Preliminary research- forms Appendix G Unit 2
Appendix G: blank forms, sample form, actual student log
How many hits, general type of therapy (cell-based, drug, etc.) Find any stem cell therapies on the market for these diseases (there may not be an example.)

4. Narrow down to one disease. Answer questions on Regenerative Medicine and Clinical Trials Research Project handout.

5. Use the information found to create a PowerPoint presentation summarizing the clinical trial results from chosen disease. (See examples of student work-Appendix H
Unit 2 Appendix H: HIV, Macular Degeneration, Spinal Cord Injury

OR

B. If you were an adult stem cell, what kind would you be?

1. Write an essay explaining why you are important, where you work, and a detailed description of how you keep the body healthy and in homeostasis.

2. Or draw all these as a cartoon/storyboard to ultimately be turned into an animation.

3. Or create a pamphlet about why you should be a certain type of adult stem cell.

IV. Assessment:

A. What are some different types of stem cells?
B. Fill out characteristics of embryonic and adult stem cells vs. progenitor cell table under Assessment in the Unit Two Appendix I: student, teacher
C. What is homeostasis and why is it important to living organisms?
D. Where have we found adult stem cells?
E. Why are scientists studying star fish (or planaria) regeneration in relation to human limbs?
F. Why do we need adult stem cells?
G. What are some of the current uses of adult stem cells?
H. What are the steps in clinical trials and what do they mean?

Additional Resources
Check Medical News Today, Wired.com, New Scientist, ScienceDaily for updates.
Powerpoints/videos about regenerative medicine; includes lesson plans, scientific animations and scientist lecture videos:
http://outreach.mcb.harvard.edu/materials.htm

HHMI Activities that go along with lectures – planaria regeneration lab
http://www.hhmi.org/biointeractive/activities/index.html

Simple pipeline diagram:
http://www.psoriasis.org/netcommunity/researchers_pipeline

More complicated FDA pipeline: Nature
http://www.nature.com/nrd/journal/v5/n6/fig_tab/nrd2033_F1.html

Where are the Cures? Valley of Death.
http://www.newsweek.com/id/166856

Using undifferentiated human Embryonic Stem Cells for therapies? NO!
http://www.cirm.ca.gov/node/2089

FDA clinical trials FAQ:
http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm121345.htm

Clinicaltrials.gov:
http://clinicaltrials.gov/ct2/info/understand

From Idea to Market: The Drug Approval Process
http://www.jabfm.org/cgi/reprint/14/5/362.pdf

Dose response curve, Merck: Eye Cells Believed To Be Retinal Stem Cells Are Misidentified
http://www.sciencedaily.com/releases/2009/03/090330200833.htm

Scientists Search Starfish For Key to Human Regeneration
http://www.wired.com/wiredscience/2007/04/scientists_sear/

Mighty Mice Regrow Organs (strain that regenerates better, trying to figure out why.)
http://www.wired.com/medtech/genetics/news/2005/09/68962#

Grow Your Own Limbs
http://www.wired.com/medtech/genetics/news/2006/09/71817?currentPage=al

Info and pictures about lizard tail regeneration – easy
http://www.factmonster.com/dk/encyclopedia/reptiles.html

Info about adult stem cells from NIH
http://stemcells.nih.gov/info/basics/basics5.asp

Animation on homeostasis
http://health.howstuffworks.com/adam-200092.htm

Interactive physiology about homeostasis
http://ats.doit.wisc.edu/biology/ap/ho/ho.htm

Retinal stem cells video
http://videos.howstuffworks.com/hsw/26397-body-and-brain-retinal-stem-cells-video.htmBlood cells and stem cells
http://videos.howstuffworks.com/hsw/5953-blood-a-comparison-of-blood-cells-video.htm

Researchers Identify Major Source of Muscle Repair Cells; Implications For Treating Duchenne's Muscular Dystrophy:

<http://www.sciencedaily.com/releases/2006/01/060131085949.htm>